Roche

Pharmaceuticals

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Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

FEDERAL EXPRESS Priority #7917 0822 9101

Nutley, March 22, 1999

Re: Docket No. 98D-0994: Draft Guidance for Industry on BACPAC I

Dear Sir or Madam:

Hoffmann-LaRoche hereby encloses its comments to the Draft Guidance to Industry on BACPAC I.

Yours sincerely,

HOFFMANN-LA ROCHE INC.

David Ridge

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DNR:jw
Enclosure
HLR No. 1999-673

98D-0994

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Hoffmann-LaRoche Inc
Comments to FDA Guidance to Industry
BACPAC I: Intermediates in Drug Substance Synthesis

Note:

- Additions of new text appear in Italics.
- Suggested deletions appear as strikethroughs.

Sec.	Page	Line	Suggested Change	Comment
I	2	16	...intermediates ~~except~~ *including* the ...	Specifications for the final intermediate <u>should</u> be included in BACPAC I. It will be confusing if certain aspects of the final intermediate (i.e., process conditions leading to its formation) are included in BACPAC I while others (i.e., specifications) are not.
I	2	17	FOOTNOTE 4: ~~Changes to the final intermediate and~~ *M*anufacturing ...	BACPAC I should cover all changes up to and including the final intermediate.
II	3	76-77	...~~inform applicants of the type of the type of filing recommended~~ *provide the applicants with at least a general sense of the kinds of changes and the likely degree of impact of those changes, so that the applicant may consider the type of filing that may be required*...	Applicants need more information from DMF holder in order to make the appropriate filing.
III	4	87	...document does not ~~call for~~ *require* the...	
III	4	97	...changes *(including different salt forms)* to...	
IIIA	5	123-4	...comparing ~~three~~ postmodification batches to ~~the range of~~ historical data from ~~ten~~ premodification...	The number of pre and post modification batches considered must be flexible and appropriate for the given circumstances. Perhaps add a footnote explaining that three postmodification batches is customary, but that minor changes might be supportable with fewer batches. It is also imperative that historical data of less than 10 premodification batches not preclude the ability to make BACPAC changes. Also, the use of laboratory, as well as pilot-scale data should be considered if appropriate.
IIIA	5	128	...if ~~at least three~~ postmodification...	See comment for Sec.IIIA, Page 5, Lines 123-4.

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IIIA	5	138	...the ~~upper statistical~~ *maximum upper* limit...	There may not be sufficient data for proper statistical analysis.
IIIA	5	139	...the ~~upper statistical~~ *maximum upper* limit...	See comment for Section IIIA, Page 5, Line 138.
IIIA	6	150-1	...the ~~stated~~ *specified* limits, or if not specified, are at or below the *maximum* upper ~~statistical~~ limit ...	ICH definition of "specified impurities" should be used.
IIIA	5	152-3	...~~upper statistical~~ *maximum upper* limit...	See comment for Section IIIA, Page 5, Line 138.
IIIA	6	168	...batches *or laboratory data in certain cases.* If equivalence is demonstrated by using pilot *or laboratory* batches...	The use of laboratory data should be considered for certain types of changes, or when the commercial scale itself is small (e.g., prep lab or pilot plant).
IIIA	7	173-5	...procedures *after the final intermediate* (or repetition of an existing procedure on a routine basis) to achieve equivalence with prechange material ~~after the final intermediate~~ are...	Clarification.
IIIB	7	180	...made ~~before~~ *up to and including* the...	
IIIB	7	184	...made ~~before~~ *up to and including* the...	
IIIB	7	195	...if ~~at least three~~ postmodification...	See comment for Sec.IIIA, Page 5, Lines 123-4.
IIIB	7	200	...profile, *if pertinent.*	
IVA	8	209	...parameters *associated with site, scale, and equipment changes* should...	Original wording was contradictory to the changes provided for in Section IV.C. – Manufacturing Process Changes.
IVA	8	213	The *types of* test...	While we object to the inclusion of the general 3-batch requirement as stated above, it must not be misconstrued that demonstration batch requirements are cumulative for multiple changes.

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Sec.	Page	Line	Suggested Change	Comment
IVA	8	219-21	~~The….controls.~~	This issue is not relevant to this document. It is covered by cGMPs.
IVA	8	227	…facility *(building) or contiguous campus* that	
IVA	8	232	…documentation *for a move to a different campus or to a contract manufacturer* (filed…	
IVA	9	241	…data on ~~at least three~~ batches…	See comment for Sec. IIIA, Page 5, Lines 123-4.
IVA	9	243-5	~~Validation data . . . purpose.~~	Validation of analytical methods for intermediate steps is not provided in original NDAs and this guidance must not provide for additional regulatory burdens.
IVA	9	263-4	…owned ~~either~~ by the applicant or by a contract manufacturer, *either of which has been* previously…	Clarification
IVA	9	262-3	…if ~~the site change does not involve the final intermediate and~~ the…	BACPAC I should cover all changes up to and including the final intermediate.
IVA	9	267	~~The site change involves the final intermediate~~	BACPAC I should cover all changes up to and including the final intermediate.
IVA	10	268	… by *the applicant or* a contract…..	
IVA	10	270	… by *the applicant or* a contract…..	
IVA	10-11	273-308	Omit entire Section 2 - Scale Changes.	A separate section on scale changes is neither necessary nor appropriate. Production scale information is not typically included in NDAs, nor are we aware of existing FDA policies on bulk drug scale changes, as those provided for drug product. This guidance must therefore not provide for additional regulatory burden.

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IVA	11	313	...equipment ~~that is not significantly different~~ *of similar operating principle and material of construction* from...	Clarification
IVA	11	319-25	... is *of* significantly different *operating principle or material of construction* from that previously used, the potential for change in the impurity profile exists even when there are no modifications to process parameters. ~~Examples include switching from glass to metal reactors or changing the method of agitation for a step that depends on the mixing of heterogeneous materials.~~ A significant change of equipment *from that described in the NDA* should be filed as an amendment(s) to the master file(s) and/or in an annual report, as appropriate ~~and documented as described for scale changes.~~	Detailed equipment information is not typically filed in NDAs.
IVB	11	329	...are ~~not~~ included...	See comment for Sec.I, Page 2, Line 16.
IVB	12	341	...method *filed in the NDA* with . . .	There may be tests and methods which are not filed to the NDA but are conducted for information-gathering purposes. These must be excluded from this guidance.
IVB	12	354	...Changes *(to those already filed to the NDA)*	See comments for Sec. IVB, Page 12, Line 341
IVB	13	370	...profile ~~and physical properties~~:	Physical properties are only relevant for drug substance.
IVB	13	372	...on ~~at least three~~ batches...	See comment for Sec.IIIA, Page 5, Lines 123-4.
IVB	14	395-8	~~Changes...concurrence.~~ *Annual report (for changes involving solvents and reagents).* *Changes being effected supplement (for changes involving starting materials and intermediates).*	

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Sec.	Page	Line	Suggested Change	Comment
IVB	14	407	...procedues *reported in the NDA process description* in...	
IVC	14	413	...profile ~~and physical properties~~:	Physical properties are only relevant for drug substance.
IVC	15	415	...on ~~at least three~~ batches...	See comment for Sec.IIIA, Page 5, Lines 123-4.
IVC	15	442	~~Changes being effected supplement~~ *Annual report*	Process changes up to and including the final intermediate, where equivalence can be demonstrated, should be filable in an Annual Report.
IVC	16	454	...data on ~~at least three~~ batches...	See comment for Sec.IIIA, Page 5, Lines 123-4.
IVC	17	480-4	~~Prior approval supplement~~ *Changes being effected supplement.* ~~For route changes...filing.~~ Changes for which equivalence cannot be demonstrated must be filed for prior-approval.	
IVC	17	486	...in ~~commercial~~ availability...	It must not be implied that commercial availability is a necessary requirement for defining a starting material (see recent ICH GMP Guideline).
IVC	17	501-2	~~A list of sources (including commercial vendors and contract manufacturers) of the redefined starting material.~~	Names of commercial sources are not typically filed as part of NDA documentation. A listing of vendors might be suggested in order to support the position that the material is commercially available, but must not be misconstrued as a restriction to adding additional vendors.
IVC	18	503-5	~~An outline of the change control protocol that has been or will be followed when establishing the suitability of a new supplier or when the existing supplier's process is changed.~~	This is not relevant to this guidance. Change control is a cGMP issue, not a registration issue.
IVC	18	506	profile ~~and physical properties~~:	Physical properties are only relevant for drug substance.

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Sec.	Page	Line	Suggested Change	Comment
IVC	18	507-32	~~A report on …for guidance.~~	Delete entire section. This is information that is not customarily filed to an original NDA. Changes to starting material vendors is a change control/cGMP issue, not a review issue.
IVC	18	538	~~Changes being effected supplement.~~ *Annual Report.*	
IVD	19	541	The *type of* test…	Not applicable to the number of test batches. See comment for Sec. IV, Page 8, Lines 213-4.
Attach.	21	563	…intermediates ~~except~~ *including* the…	See comment for Sec.I, Page 2, Line 16.
Attach.	22	585	The *step wherein the* solution…	Clarification.
Attach.	22	589-93	…from ~~10~~ recent… ~~The upper statistical…on < 10 batches.)~~	The number historical batches considered must be flexible and appropriate for the given circumstances. If possible, data on the 10 most recent batches should be reviewed. See comment from Sec. IIIA, Page 5, Lines 138-9.
Attach.	24	642	…~~are usually~~ *may be* available…	Commercial availability is not a necessary requirement for a starting material (see recent ICH GMP guideline).
Attach.	24		Add ICH definition for "specified impurity".	See comment for Section IIIA, Page 5, Lines 150-1.

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